# Clinical trial results:
# A Randomized, Double-Blind, Placebo-Controlled Parallel Group Study to Investigate the Safety and Efficacy of Arbaclofen Extended-Release Tablets for the Treatment of Spasticity in Patients with Multiple Sclerosis (Study OS440-3004)

## Summary

| | |
|---|---|
| EudraCT number | 2017-004100-22 |
| Trial protocol | BG PL HR |
| Global end of trial date | 03 December 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 30 November 2020 |
| First version publication date | 30 November 2020 |
| Summary attachment (see zip file) | OS440-3004 CSR Synopsis (OS440-3004_Clinical Study Report Synopsis [05-JUN-2020].pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | OS440-3004 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03290131 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Osmotica Pharmaceutical US LLC |
| Sponsor organisation address | 400 Crossing Boulevard, Bridgewater, United States, NJ 08807 |
| Public contact | Meredith Velasco, Osmotica Pharmaceutical US LLC, +1 908809 1423, mvelasco@osmotica.com |
| Scientific contact | Meredith Velasco, Osmotica Pharmaceutical US LLC, +1 908809 1423, mvelasco@osmotica.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 03 December 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 December 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 December 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the safety and efficacy of Arbaclofen Extended-Release Tablets (AERT) for treatment of spasticity in patients with Multiple Sclerosis (MS).

Protection of trial subjects:

This study was performed in accordance with Good Clinical Practice standards.

Before undertaking any study-related procedures with subjects, the purpose and nature of the study, as well as possible adverse effects, were explained to them in understandable terms and written informed consent was obtained from each individual.

An independent, chartered Data Safety Monitoring Board (DSMB) reviewed all safety data on 4 occasions during the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 31 January 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 54 |
| Country: Number of subjects enrolled | Croatia: 20 |
| Country: Number of subjects enrolled | Bulgaria: 57 |
| Country: Number of subjects enrolled | Belarus: 33 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 21 |
| Country: Number of subjects enrolled | Moldova, Republic of: 12 |
| Country: Number of subjects enrolled | Russian Federation: 149 |
| Country: Number of subjects enrolled | Serbia: 30 |
| Country: Number of subjects enrolled | Ukraine: 135 |
| Country: Number of subjects enrolled | United States: 25 |
| Worldwide total number of subjects | 536 |
| EEA total number of subjects | 131 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 531 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

First subject enrolled on 13 Feb 2018; last subject completed on 03 Dec 2018. Total of 536 subjects were enrolled at 82 sites in the United States and Central and Eastern Europe (Russia, Belarus, Serbia, Bosnia and Herzegovina, Croatia, Bulgaria, Moldova, Poland, and Ukraine).

### Pre-assignment

Screening details:

Eligible subjects underwent up to a 21-day washout period for withdrawal of anti-spasticity and/or muscle relaxation medications before randomization. Eligibility was confirmed before randomization (Visit 2). 594 subjects were screened; 58 subjects were screen failures (39 due to inclusion/exclusion criteria not met); 536 subjects were randomized.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Every effort was made to retain the integrity of the blind. The study medication was identical in appearance for all subjects, regardless of treatment assignment.

No premature unblinding occurred during the study. The study blind was broken at study completion once the following were met: 1) Database was locked and 2) the statistical analysis plan (SAP) was finalized.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | AERT 40 mg |

Arm description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 40 mg (20 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 40 mg arm.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Arbaclofen extended-release tablets |
| Investigational medicinal product code | |
| Other name | AERT, arbaclofen ER tablets |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

AERT was supplied as blue, round biconvex tablets in blister card wallets with matching placebo tablets. IMP was administered as follows:
- Days 1 to 6: AERT 20 mg/day given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening
- Days 7 to 84: AERT 40 mg/day given as one placebo tablet and one 20-mg AERT in both the morning and the evening
- Days 85 to 88: AERT 20 mg/day given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening
- Days 89 to 91: AERT 0 mg/day given as two placebo tablets both in the morning and the evening.

| | |
|---|---|
| **Arm title** | AERT 80 mg |

Arm description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 80 mg (40 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were

randomized to the AERT 80 mg arm.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Arbaclofen extended-release tablets |
| Investigational medicinal product code | |
| Other name | AERT, arbaclofen ER tablets |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

AERT was supplied as blue, round biconvex tablets in blister card wallets with matching placebo tablets. IMP was administered as follows:
- Days 1 to 3: AERT 20 mg/day given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening
- Days 4 to 6: AERT 40 mg/day given as one placebo tablet and one 20-mg AERT both in the morning and the evening
- Days 7 to 9: AERT 60 mg/day was given as one placebo tablet and one 20-mg AERT in the morning and two 20-mg AERT in the evening
- Days 10 to 84: AERT 80 mg/day was given as two 20-mg AERT both in the morning and the evening
- Days 85 to 88: AERT 40 mg/day was given as one placebo tablet and one 20-mg AERT both in the morning and the evening
- Days 89 to 91: AERT 20 mg/day was given as two placebo tablets in the morning and one placebo tablet and one 20-mg AERT in the evening

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo arm: placebo tablets administered twice daily.

Results are presented for the Intent-to-Treat (ITT) population, which includes all 178 subjects who were randomized to the placebo arm.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo tablets were supplied as blue, round biconvex tablets that matched the AERT tablets and were packaged in blister card wallets. From Days 1 to 91, two placebo tablets were administered both in the morning and the evening.

| **Number of subjects in period 1** | AERT 40 mg | AERT 80 mg | Placebo |
|---|---|---|---|
| Started | 179 | 179 | 178 |
| Completed | 137 | 107 | 159 |
| Not completed | 42 | 72 | 19 |
| Adverse event, non-fatal | 22 | 57 | 11 |
| Subject moved to another city | - | 1 | - |
| Subject request | 18 | 13 | 8 |
| MS relapse | 2 | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | AERT 40 mg |
| Reporting group description: | |
| Experimental therapy arm: arbaclofen extended-release tablets (AERT) 40 mg (20 mg twice daily).<br><br>Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 40 mg arm. | |
| Reporting group title | AERT 80 mg |
| Reporting group description: | |
| Experimental therapy arm: arbaclofen extended-release tablets (AERT) 80 mg (40 mg twice daily).<br><br>Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 80 mg arm. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo arm: placebo tablets administered twice daily.<br><br>Results are presented for the Intent-to-Treat (ITT) population, which includes all 178 subjects who were randomized to the placebo arm. | |

| Reporting group values | AERT 40 mg | AERT 80 mg | Placebo |
|---|---|---|---|
| Number of subjects | 179 | 179 | 178 |
| Age categorical | | | |
| For the ITT population, the overall mean (SD) age at baseline was 46.5 (9.60) years (range, 21 to 65 years). The results for age were generally balanced across the treatment groups. | | | |
| Units: Subjects | | | |
| Adults (18-65 years) | 179 | 179 | 178 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 46.0 | 46.0 | 47.5 |
| standard deviation | ± 9.50 | ± 9.71 | ± 9.55 |
| Gender categorical | | | |
| For the ITT population, the majority of subjects were female (59.5%). The results for gender were generally balanced across treatment groups. | | | |
| Units: Subjects | | | |
| Female | 108 | 101 | 110 |
| Male | 71 | 78 | 68 |
| Race | | | |
| For the ITT population, the majority of subjects were white (97.4%). The results for race were generally balanced across treatment groups. | | | |
| Units: Subjects | | | |
| Asian | 0 | 0 | 1 |
| Black or African American | 4 | 0 | 2 |
| White | 171 | 177 | 174 |
| More than one race | 1 | 0 | 1 |
| Missing | 3 | 2 | 0 |
| MS Subtype | | | |
| For the ITT population, the MS subtype at baseline was relapsing-remitting (RR) for the majority of subjects (323 subjects; 60.3%); 186 subjects (34.7%) had secondary progressive (SP) MS and 27 subjects (5.0%) had primary progressive (PP) MS. The results for MS subtype were generally balanced across treatment groups. | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Relapsing remitting | 117 | 100 | 106 |
| Primary progressive | 9 | 8 | 10 |
| Secondary progressive | 53 | 71 | 62 |
| Weight | | | |
| For the ITT population, the overall mean (SD) weight at baseline was 70.85 (15.182) kg (range, 36.5 to 126.0 kg). The results for weight were generally balanced across treatment groups. | | | |
| Units: kg | | | |
| arithmetic mean | 70.38 | 71.45 | 70.71 |
| standard deviation | ± 15.371 | ± 15.405 | ± 14.825 |
| Body Mass Index | | | |
| For the ITT population, the overall mean (SD) BMI at baseline was 24.648 (4.6036) kg/m2 (range, 16.23 to 42.52 kg/m2). Results for BMI were generally balanced across treatment groups. | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 24.661 | 24.660 | 24.623 |
| standard deviation | ± 5.1229 | ± 4.2615 | ± 4.4048 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 536 | | |
| Age categorical | | | |
| For the ITT population, the overall mean (SD) age at baseline was 46.5 (9.60) years (range, 21 to 65 years). The results for age were generally balanced across the treatment groups. | | | |
| Units: Subjects | | | |
| Adults (18-65 years) | 536 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| For the ITT population, the majority of subjects were female (59.5%). The results for gender were generally balanced across treatment groups. | | | |
| Units: Subjects | | | |
| Female | 319 | | |
| Male | 217 | | |
| Race | | | |
| For the ITT population, the majority of subjects were white (97.4%). The results for race were generally balanced across treatment groups. | | | |
| Units: Subjects | | | |
| Asian | 1 | | |
| Black or African American | 6 | | |
| White | 522 | | |
| More than one race | 2 | | |
| Missing | 5 | | |
| MS Subtype | | | |
| For the ITT population, the MS subtype at baseline was relapsing-remitting (RR) for the majority of subjects (323 subjects; 60.3%); 186 subjects (34.7%) had secondary progressive (SP) MS and 27 subjects (5.0%) had primary progressive (PP) MS. The results for MS subtype were generally balanced across treatment groups. | | | |
| Units: Subjects | | | |
| Relapsing remitting | 323 | | |
| Primary progressive | 27 | | |
| Secondary progressive | 186 | | |

| | | | |
|---|---|---|---|
| Weight | | | |
| For the ITT population, the overall mean (SD) weight at baseline was 70.85 (15.182) kg (range, 36.5 to 126.0 kg). The results for weight were generally balanced across treatment groups. | | | |
| Units: kg<br>arithmetic mean<br>standard deviation | -<br> | | |
| Body Mass Index | | | |
| For the ITT population, the overall mean (SD) BMI at baseline was 24.648 (4.6036) kg/m2 (range, 16.23 to 42.52 kg/m2). Results for BMI were generally balanced across treatment groups. | | | |
| Units: kg/m2<br>arithmetic mean<br>standard deviation | -<br> | | |

## End points

### End points reporting groups

| Reporting group title | AERT 40 mg |
|---|---|

Reporting group description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 40 mg (20 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 40 mg arm.

| Reporting group title | AERT 80 mg |
|---|---|

Reporting group description:

Experimental therapy arm: arbaclofen extended-release tablets (AERT) 80 mg (40 mg twice daily).

Results are presented for the Intent-to-Treat (ITT) population, which includes all 179 subjects who were randomized to the AERT 80 mg arm.

| Reporting group title | Placebo |
|---|---|

Reporting group description:

Placebo arm: placebo tablets administered twice daily.

Results are presented for the Intent-to-Treat (ITT) population, which includes all 178 subjects who were randomized to the placebo arm.

### Primary: Co-primary Efficacy Endpoint: TNmAS-MAL in the ITT Population

| End point title | Co-primary Efficacy Endpoint: TNmAS-MAL in the ITT Population |
|---|---|

End point description:

The Total Numeric-transformed modified Ashworth Scale (TNmAS) is considered the primary clinical measure of muscle spasticity in subjects with neurological conditions. It consists of a 6-point rating scale to measure abnormality in tone or the resistance to passive movements.

The TNmAS assessment was to be performed by the study evaluator (someone other than the Investigator) who had been appropriately trained to perform and assess the TNmAS, and when possible all TNmAS assessments were performed for a particular subject by the same study evaluator throughout the study.

The outcome variable for TNmAS-MAL was least-squares (LS) mean change from baseline (and 95% confidence interval [CI]) to Day 84 in the ITT population by treatment group. AERT 40 mg was compared with placebo first (for both co-primary endpoints, TNmAS-MAL and CGIC). Both co-primary endpoints had to meet the 0.05 level for AERT 40 mg vs placebo for the study to be considered a success.

| End point type | Primary |
|---|---|

End point timeframe:

TNmAS score of the most affected limb (TNmAS-MAL) was recorded at screening (Visit 1), baseline (Visit 2), Day 42 (Visit 4), Day 84 (Visit 5), and Day 92 (final visit or early termination).

| End point values | AERT 40 mg | AERT 80 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 139 | 115 | 164 | |
| Units: Change from baseline to Day 84 | | | | |
| least squares mean (confidence interval 95%) | -1.67 (-1.97 to -1.36) | -1.79 (-2.12 to -1.46) | -1.28 (-1.57 to -0.99) | |

## Statistical analyses

| **Statistical analysis title** | LS mean difference for AERT 40 mg vs placebo |
|---|---|

Statistical analysis description:

Least-squares mean were used to compare AERT 40 mg vs placebo. The TNmAS-MAL was analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, visit, country, and the treatment-by-visit interaction; and with baseline score as a covariate.

There was statistically significant greater improvement from baseline to Day 84 in TNmAS-MAL scores in the AERT 40 mg group compared to the placebo group.

| | |
|---|---|
| Comparison groups | AERT 40 mg v Placebo |
| Number of subjects included in analysis | 303 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0482 [1] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.77 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.196 |

Notes:

[1] - p-value calculated for AERT 40 mg LS mean - placebo LS mean.

| **Statistical analysis title** | LS mean difference for AERT 80 mg vs placebo |
|---|---|

Statistical analysis description:

Least-squares mean were used to compare AERT 80 mg versus placebo. The TNmAS-MAL was analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, visit, country, and the treatment-by-visit interaction; and with baseline score as a covariate.

There was statistically significant greater improvement from baseline to Day 84 in TNmAS-MAL scores in the AERT 80 mg group compared to the placebo group.

| | |
|---|---|
| Comparison groups | AERT 80 mg v Placebo |
| Number of subjects included in analysis | 279 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0118 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.51 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.91 |
| upper limit | -0.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.203 |

Notes:

[2] - p-value calculated for AERT 80 mg LS mean - placebo LS mean.

## Primary: Co-primary Efficacy Endpoint: CGIC in the ITT Population

| | |
|---|---|
| End point title | Co-primary Efficacy Endpoint: CGIC in the ITT Population |

End point description:

For the CGIC, the Investigator rated the change in overall global functional performance (not limited to spasticity) the subject was experiencing (based on assessment of the subject since Visit 2). The Investigator evaluated the subject's status on a -3 to +3 scale judging whether there had been a change from significantly worse (-3) to significantly improved (+3) relative to baseline (Visit 2) and had to have access to the TNmAS.

The outcome variable was LS mean CGIC score (and 95% CI) at Day 84 in the ITT population by treatment group. AERT 40 mg was compared with placebo first (for both co-primary endpoints, TNmAS-MAL and CGIC). Both co-primary endpoints had to meet the 0.05 level for AERT 40 mg vs placebo for the study to be considered a success.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

The CGIC was recorded at Day 42 (Visit 4), Day 84 (Visit 5), and Day 92 (final visit or early termination).

| **End point values** | AERT 40 mg | AERT 80 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 140 | 115 | 164 | |
| Units: Score | | | | |
| least squares mean (confidence interval 95%) | 0.36 (0.17 to 0.54) | 0.01 (-0.19 to 0.22) | 0.45 (0.27 to 0.63) | |

### Statistical analyses

| **Statistical analysis title** | LS mean difference for AERT 40 mg vs placebo |
|---|---|

Statistical analysis description:

Least-squares mean were used to compare AERT 40 mg versus placebo. The CGIC was analyzed using a REML-based MMRM with fixed effects for treatment, visit, country, and the treatment-by-visit interaction. Because the CGIC is a change score, no value was measured at baseline.

No statistically significant difference in the mean CGIC score was observed between the placebo group and the AERT 40 mg group.

| | |
|---|---|
| Comparison groups | AERT 40 mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 304 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4272 [3] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.121 |

Notes:

[3] - p-value calculated for AERT 40 mg LS mean - placebo LS mean.

| **Statistical analysis title** | LS mean difference for AERT 80 mg vs placebo |
|---|---|

Statistical analysis description:

Least-squares mean were used to compare AERT 80 mg versus placebo. The CGIC was analyzed using a REML-based MMRM with fixed effects for treatment, visit, country, and the treatment-by-visit interaction. Because the CGIC is a change score, no value was measured at baseline.

A statistically significant difference in the mean CGIC score was observed between the placebo group and the AERT 80 mg group.

| | |
|---|---|
| Comparison groups | AERT 80 mg v Placebo |
| Number of subjects included in analysis | 279 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 [4] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.69 |
| upper limit | -0.19 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.126 |

Notes:

[4] - p-value calculated for AERT 80 mg LS mean - placebo LS mean.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from time of informed consent through completion of the last study visit. A treatment-emergent AE was any AE with onset or worsening on or after the first dose of study drug up until 30 days after the last dose of study drug.

Adverse event reporting additional description:

Adverse events could have been reported spontaneously by the subject or observed by the Investigator.

Within each preferred term, subjects were counted only once if they had more than one AE reported during the treatment period.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | AERT 40 mg |

Reporting group description:

Adverse event results are presented for the Safety population, which includes all subjects who received at least 1 dose of double-blind study treatment and had at least 1 postdose visit. The Safety population includes all 179 subjects who were randomized to the AERT 40 mg arm.

All serious TEAEs that occurred are reported. Non-serious TEAEs that occurred in 5% or more of subjects in any treatment group are reported.

No deaths occurred during the study.

| | |
|---|---|
| Reporting group title | AERT 80 mg |

Reporting group description:

Adverse event results are presented for the Safety population, which includes all subjects who received at least 1 dose of double-blind study treatment and had at least 1 postdose visit. The Safety population includes all 179 subjects who were randomized to the AERT 80 mg arm.

All serious TEAEs that occurred are reported. Non-serious TEAEs that occurred in 5% or more of subjects in any treatment group are reported.

No deaths occurred during the study.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Adverse event results are presented for the Safety population, which includes all subjects who received at least 1 dose of double-blind study treatment and had at least 1 postdose visit. The Safety population includes all 178 subjects who were randomized to the placebo arm.

All serious TEAEs that occurred are reported. Non-serious TEAEs that occurred in 5% or more of subjects in any treatment group are reported.

No deaths occurred during the study.

| Serious adverse events | AERT 40 mg | AERT 80 mg | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 179 (3.35%) | 6 / 179 (3.35%) | 6 / 178 (3.37%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Schwannoma | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 0 / 179 (0.00%) | 1 / 178 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 179 (0.56%) | 0 / 179 (0.00%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 179 (0.56%) | 0 / 179 (0.00%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint injury | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 1 / 179 (0.56%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Multiple sclerosis relapse | | | |
| subjects affected / exposed | 2 / 179 (1.12%) | 3 / 179 (1.68%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 1 / 179 (0.56%) | 0 / 179 (0.00%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 0 / 179 (0.00%) | 1 / 178 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trigeminal neuralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 179 (0.00%) | 0 / 179 (0.00%) | 1 / 178 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 179 (0.56%) | 0 / 179 (0.00%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 0 / 179 (0.00%) | 1 / 178 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 1 / 179 (0.56%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 1 / 179 (0.56%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 179 (0.56%) | 0 / 179 (0.00%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 0 / 179 (0.00%) | 1 / 178 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delirium | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 179 (0.56%) | 0 / 179 (0.00%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 1 / 179 (0.56%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somatic symptom disorder | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 1 / 179 (0.56%) | 0 / 178 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 179 (0.00%) | 0 / 179 (0.00%) | 1 / 178 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | AERT 40 mg | AERT 80 mg | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 137 / 179 (76.54%) | 146 / 179 (81.56%) | 126 / 178 (70.79%) |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 25 / 179 (13.97%) | 33 / 179 (18.44%) | 19 / 178 (10.67%) |
| occurrences (all) | 25 | 33 | 19 |
| Somnolence | | | |
| subjects affected / exposed | 18 / 179 (10.06%) | 26 / 179 (14.53%) | 17 / 178 (9.55%) |
| occurrences (all) | 18 | 26 | 17 |
| Headache | | | |
| subjects affected / exposed | 2 / 179 (1.12%) | 6 / 179 (3.35%) | 12 / 178 (6.74%) |
| occurrences (all) | 2 | 6 | 12 |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 23 / 179 (12.85%) | 33 / 179 (18.44%) | 27 / 178 (15.17%) |
| occurrences (all) | 23 | 33 | 27 |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 179 (1.12%) | 14 / 179 (7.82%) | 6 / 178 (3.37%) |
| occurrences (all) | 2 | 14 | 6 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 179 (2.23%) | 9 / 179 (5.03%) | 6 / 178 (3.37%) |
| occurrences (all) | 4 | 9 | 6 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 39 / 179 (21.79%) | 27 / 179 (15.08%) | 28 / 178 (15.73%) |
| occurrences (all) | 39 | 27 | 28 |
| Vomiting | | | |
| subjects affected / exposed | 13 / 179 (7.26%) | 18 / 179 (10.06%) | 16 / 178 (8.99%) |
| occurrences (all) | 13 | 18 | 16 |
| Renal and urinary disorders | | | |
| Urinary tract disorder | | | |
| subjects affected / exposed | 48 / 179 (26.82%) | 54 / 179 (30.17%) | 61 / 178 (34.27%) |
| occurrences (all) | 48 | 54 | 61 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 39 / 179 (21.79%) | 39 / 179 (21.79%) | 27 / 178 (15.17%) |
| occurrences (all) | 39 | 39 | 27 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 September 2017 | The following changes were made to Protocol CLN.OS440-3004.PR.A01 as Amendment 1 dated 19 September 2017:<br><br>- Clarified birth control requirements for subjects and partners of subjects.<br>- Clarified that "high dose (120 mg daily)" oral or intravenous methylprednisolone or equivalent within 3 months before Visit 1 (Screening) would be exclusionary.<br>- Added a criterion excluding subjects with clinically significant abnormal laboratory values at Screening.<br>- Added taper and washout periods for specific anti-spasticity and/or muscle relaxation medications.<br>- Corrected the mistake in the original protocol regarding a 4-point change in total USP score by replacing "A reduction of 4 points…" with "An increase of 4 points..."<br>- In the sample size calculation, specified that the determination of sample size should be based on the AERT 40 mg/day dose, as the AERT 40 mg/day dose will be analyzed first versus placebo. |
| 09 November 2017 | The following changes were made to Protocol CLN.OS440-3004.PR.A02 as Amendment 2 dated 09 November 2017:<br><br>- Disallowed subjects who experienced an acute MS exacerbation/relapse during study OS440-3004 from enrolling in study OS440-3005. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported